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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/989,896	12/12/1997	MATHIAS GEHRMANN	05552.1337-0	9415

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EXAMINER
SAUNDERS, DAVID A

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
989 896	GEHRMANN et al.
Examiner	**Group Art Unit**
SAUNDERS	1674

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 10/9/01.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-22 and 25-33 is/are pending in the application.

Of the above claim(s) 14-22 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-13 and 25-33 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 21

☐ Interview Summary, PTO-413

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

The amendment of 10/9/01 (Paper 23) has been entered. Claims 1-22 and 25-33 are pending; claims 1-13 and 25-33 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's amendment has overcome the previously stated 112, second paragraph rejection.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant has not shown that the L6 antibody or the hybridoma secreting it are publically available.

Applicant has urged that two journal articles of Hellstrom et al. show that the antibody was publically available. This is unconvincing because there is no evidence on record that these journals have a policy of requiring authors to provide described material without restriction to the public. Even if the journals had such a policy, it would need to be shown that maintenance of the hybridoma is required of authors to at least the degree set forth in 37 CFR 1.806. It is suggested that applicant determine whether the L6 antibody of Hellstrom et al., has been deposited in order to enable the claims of a U.S. patent.

Claims 1-13 and 25-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims reciting constructs having the specifically

exemplified internal linkers (i.e. internal to the sFv) does not reasonably provide enablement for claims encompassing constructs having any and all internal linkers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Applicant's response of Paper 23 has failed to overcome this rejection of record.

Applicant's response (page 3) has noted that the traversal of the 103 rejection of record was stated with respect to the linkers internal to the sFv. Since applicant has thus admitted on the record that one could not provide the internal linkers of the claimed construct without undue experimentation, no claim is enabled unless it is limited to recite the sequence of the internal linkers exemplified.

All of what follows in applicant's traverse at page 3 is merely an argument that the specification adequately teaches one how to provide appropriate linkers between the antigen binding region and the enzyme. Since these linkers are not internal to the sFv, applicant's urgings are unconvincing.

Applicant's amendment has necessitated the following new rejection.

Claims 1-13 and 25-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 has been amended to recite "the antigen

binding regions comprise a single polypeptide". This is new matter because it is broader than "the antigen binding region(s) is composed of a single polypeptide". MPEP 2111.03.

Claims 1-9, 25-27, 30 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al. (Brit J. Can. 65, 235, 1992) or Seemann et al. (EP 0,501,215 or CA 2,062,047 in view of Huston et al. (5,132,405) and, as necessary, Bosslet et al. (EP 0,040,097 or US 5,591,828) and Eaton et al. (EP 0,392,745), for reasons of record.

Claims 1-2, 9, 11-12 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al. or Seemann et al. in view of Huston et al. And, as necessary, Bosslet et al. and Eaton et al. as applied to claims 1-9, 25-27, 30 and 33 above, and further in view of Ong et al., (Can. Res. 51, 619, 1991), Bagshawe et al. (WO 89/10140) and Huston et al. (Meth. Enz., 204,46, 1991), for reasons of record.

Claims 1, 10, 13 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al. or Seemann et al. In view of Huston et al. and, as necessary, Bosslet et al. and Eaton et al. and further in view of Ong et al. Bagshawe et al. and Huston et al. as applied to claims 1, 11-12 and 31-32 above, and further in view of Goochee et al. (Biotechnol., 9, 1347, 1991) for reasons of record.

Claims 1, 6 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al. Or Seemann et al., in view of Huston et al. and, as necessary Bosslet et al. and Eaton et al. as applied to claim 1 above, and further in view of Bagshawe et al. (WO 88/07378),

Applicant's response (Paper 23) has argued that the combination of Bosslet et al. or Seemann et al. in view of Huston et al., employed to reject independent claim 1, does not make a prima facia case of obviousness. Applicant's arguments are essentially that one would not have been motivated to replace the Fab of Bosslet et al. or Seemann et al. with the sFv of Huston et al. (pages 4-5).

Applicant's argument (page 5) that Huston et al. do not teach constructs which contain a single chain enzyme is unconvincing. This is merely an argument which considers the reference in isolation from Seeman et al. and Bosslet et al. Since Huston et al. teach that the sFv may be fused to the enzyme, one would have readily envisioned that the enzyme at least in part is encoded by the same strand of nucleic acid that encodes the sFv. Further, nothing in applicant's claims requires the "pro-drug activating" enzyme" to be composed of a single polypeptide chain.

Applicant has further urged (pages 6-7) that Huston et al. only showed binding activity of an sFv construct and never demonstrated that a fused prodrug activating enzyme (or any enzyme) would be active, and that only applicant has shown that one could provide a construct having the antigen binding activity of sFv regions and the pro-drug metabolizing activity of an emyzme. This argument is found unconvincing because one would have reasonably expected the sFv portion of the fusion protein to correctly fold into a domain with antigen binding activity and the enzyme portion to correctly fold into a domain with emyzmatic activity. See Huston et al. at col. 3, line 53 - col. 4, line 37, as well as claims 1 and 3, which must be presumed to be valid.

Applicant's argument (page 7) that it is difficult to raise antibodies to tumor antigens is bogus, since at the time of applicant's invention the art was replete with moncoloral/chimeric/humanized antibodies with binding specificity for tumor antigens, and one would have been capable of redisigning the binding sites of any of these into active sFv fragments by following the teachings of Huston et al. Further, applicant's claims 1-3, 6-13 and 22-33 are not limited to anti-tumor binding constructs.

Applicant's argument (page 7) regarding the fact that treatments with antitumor antibodies often leads to selection of variant tumor cells so that the antibody is no longer effective is another bogus argument. This is a problem that can be associated with any form of tumor therapy involving use of an immunological binding agent (antibody, antibody fragment, sFv, etc.), and applicant's disclosure has contributed absolutely nothing to overcome this art recognized problem. That applicant's specification examples may have shown treatment of a particular type of tumor, at a particular stage, in a particular strain of mice is only indicative that a cure can be effected under these particular experimental conditions, which have a much reduced level of complexity in comparison to the treatment of spontaneous tumors in out bred populations, such as with humans.

Applicant has next argued (pages 7-8) that Seeman et al. and Bosslet et al. teach away from the invention by requiring, that the tumor binding portion of their construct should be as "similar as possible to the original TuMAb in the binding properties". Since Huston et al. teach that antibodies can be engineered to provide sFv constructs within antigen binding activity, there

is no reason to consider that Seeman et a. or Bosslet et al. teach away from forming sFv containing constructs. All that is necessary according to their teachings is that the binding properties of the starting antibody be retained, and such can be accomplished by following the teachings of Huston et al.

Applicant's argument (pages 7-8) that Huston et al. teach away from the instant invention by teaching constructs that do not comprise a constant domain merely confuses the record. The examiner considers the teachings of Huston et al to, in fact, be consistent with applicant's invention. The constant domains/regions referred to be Huston et al. are immunoglobulin domains/constant regions (e.g. CL-CH1, CH2-CH2, CH3-CH3). Applicant's own invention likewise has no immunoglobulin constant regions. If applicant considers the prodrug activating enyzme to constitute a "constant" region, it is certainly not an immunoglobulin constant region of the type referred to by Huston et al. Furthermore Huston et al. direct one to provide constructs in which the sFv fused to another active protein, such as an enyzme (col. 3, line 53 - col. 4, line 37), which, likewise, would not be considered as an immunoglobulin constant region.

Applicant's argument (pages 9-10) that there is no motivation to combine Huston et al. with Bosslet et al. or Seeman et al. and that the motivation to do so is only in the instant specification is unconvincing. The motivational reasons set forth previously by the examiner (Paper 26, pages 5-6) were set forth by referring to the teachings of the cited references of the cited references and/or by scientific reasoning and not by referring to applicant's own disclosure. The rest of the arguments set forth urge that because Huston et al. teach sFv constructs are

"preferably free of constant regions" one would not use the antibody fragments of Seeman et al./Bosslet et al. This argument is without foundation because neither Seeman et al. nor Bosslet et al. teach that the constant region of their Fab containing constructs is necessary for activities of antigen binding or of enzyme activity. Thus the fact that Huston et al. teach that sFv constructs should not contain immunoglobulin constant regions would not deter one from providing an sFv in lieu of the Fab of Seeman et al./Bosslet et al.

The arguments set forth at pages 10-12 regarding the tertiary references, do not overcome obviousness. The Bosslet et al. patent (tertiary reference) is not inconsistent with Huston et al., for the same reasons noted supra regarding Bosslet et al. (primary reference) and Seeman et al.

Applicant has argued that the B-lactamase of Eaton et al. provides various degradation products with no precise structure, in contrast to applicant's invention. The examiner finds that no claim requires formation of a "precise" product by action of the enzyme. It is further noted that applicant's specification page 3 indicates the enzymes of EP 0,392,745 as among those preferred.

Applicant's argument that Ong et al. and Bagshawe et al. only teach glycosylation of full monoclonal antibodies or F(ab')2 fragments merely argues these references in isolation and does not overcome the expectation that by glycosylating sFv constructs one would improve clearance. See also Paper 20 at page 15.

With respect to arguments regarding Goochee et al., see Paper 20 at page 16.

Applicant's urgings filed 10/9/01 have been considered but are unconvincing.

Due to the issuing of a new reference, a new ground of rejection follows.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action.

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-4, 8-9, 25-26 and 33 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Winter et al. (6,248,516).

Winter et al. teach constructs containing single domain ligands and therapeutic compositions and uses thereof. The single domain ligands include sFvs (col. 11, lines 38-61, espec. lines 55-58; also col. 13, lines 52-55).

The single domain ligands of Winter et al. can be linked to an effector molecule, such as an enzyme which activates a prodrug (col. 4, lines 53-56), and such linkage may be achieved by forming a fusion product, with or without a linker peptide (col. 5, lines 45-52 and col. 12, lines 4-12).

Winter et al. further teach that the constructs may contain multiple single domain ligands, which can be linked to an effector molecule (col. 5, lines 42-44), which as discussed above can be a prodrug activating enzyme. Winter et al., teach that providing constructs with multiple copies of the same ligand provides for a larger molecule which is less readily filtered from the circulation by the kidneys (col. 5, lines 36-38). The constructs can also be provided with two

single domain ligands against different epitopes of an antigen, or against different antigens, in order to enhancing binding to cell surfaces (col. 5, lines 24-35). Applicant's claim 1 encompasses either the case in which both antigen binding regions have the same binding specificity or the case in which each has a different binding specificity.

Anticipation is stated on the basis that all of what is claimed is taught within the four corners of the reference. Obviousness is stated in case applicant considers that one would have had to arrive at the instant invention by choosing from multiple options disclosed by Winter et al.

Regarding dependent claim features not discussed supra, note that for claims 2 and 9 Winter et al. teach expression of the constructs in mouse myeloma cells (e.g. col. 19, lines 59-62); these would inherently glycosylate any expressed fusion protein.

With respect to claim 4, note Winter et al. teach the constructs can be used to treat tumors (col. 4, lines 43, 62; col. 5, line 33).

Claims 1-2, 4-5, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Seeman et al. (EP 0,501,215 or CA 2,062,047).

Winter et a. have been discussed supra for teaching constructs containing multiple sFv regions, that bind to tumor cells, fused to a pro-drug activating enzyme. Winter et al. to not teach specific tumor antigens or specific pro-drug activating enzymes.

Seeman et al. teach therapeutic fusion proteins with binding specificity for CEA and with human B-glucuronidase activity. Since CEA is a known tumor antigen and since human B-

gluauonidase is a known prodrug activating enzyme, provision of these particular features in the single domain ligand constructs of Winter et al. would have been obvious.

Regarding claims 2 and 9, expression in BHK cells, as taught by Seeman et al. (page 10) would inherently yield glycosylated fusion proteins.

Claims 1, 6, 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Eaton et al.

Winter et al's. teachings have been discussed supra. They do not teach B-lactamase as a prodrug activating enzyme. Eaton et al. teach that such enzymes were art known in antibody enzyme conjugates. They teach the B-lactamase from B. Cerus (page 4, line 14). Thus it would have been obvious to provide this enzyme in the single domain ligand compositions of Winter et al.

Claims 1, 6 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Bagshawe et al. (WO 88/07378).

Winter et al's. teachings have been reviewed supra. They do not teach carboxypeptidase G2 from pendomonas as a prodrug activating enzyme. Bagshawe et al. show that this was a known prodrug activating enzyme in antibody enzyme conjugates. It hence would have been obvious to provide this enzyme the single domain ligand composition of Winter et al.

Claims 1-2, 9, 11-12 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Ong et al. and Bagshawe et al. (WO 89/10140).

Winter et al. teach that their constructs may be produced in bacteria (col. 11, lines 8-11). As previously noted (paper 20, page 8) one would have recognized that any fusion protein construct produced by bacteria would not be glycosylated.

Ong et al. teach that it is advantageous to permit rapid clearing of circulating therapeutic antibodies in a treated individual be providing galactosyl moieties on the antibodies. These authors particularly teach that such clearing would be advantageous in cases wherein antibody-enzyme conjugates that convert a prodrug to an active drug are employed. Since, antibody-enzyme conjugates and sFv-enzyme fusion proteins are functionally equivalent it would have been obvious to provide galactosyl moieties on sFv-enzyme fusion proteins, so that these could be rapidly cleared from the circulation. One of ordinary skill would have known that when a polypeptide is expressed in a prokaryote, such as E. Coli (taught by Winter et al.) there is no glycosylation, and hence, such an expressed polypeptide could be subsequently glycosylated with galactose moieties according to a chemical method, such as that taught by Ong et al. (page 1620, col. 1).

Bagshawe et al. will also be relied upon for teaching the desirability of placing galactosyl and/or mannosyl moieties on an antibody that is a member of an antibody-prodrug activating enzyme conjugate. See page 9, lines 1-5 and page 10, lines 6-25. The blocking and clearing strategy taught therein is akin to that taught by Ong et al. at pages 1622-1624. From the teachings of Ong et al. and Bagshawe et al., either together or each alone, one would have ample

motivation to provide galactosyl or other carbohydrates residues taught Bagshawe et al. (page 13) on the sFv-enzyme fusion proteins, of Winter et al.

Claims 1, 10, 13 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winter et al. in view of Ong et al., and Bagshawe et al. as applied to claims 1-2, 9, 11-12 and 31-32 above, and further in view of Goochee et al.

The above rejections have noted that one would have realized that it would have been desirable to provide a galactosylated or mannosylated polypeptide in order to enhance clearance of unbind peptide from the circulation.

Goochee et al. at page 7 show that it was known that yeast could be used to express polypeptide having a high degree of mannosylation and having a rapid clearance rate. It hence would have been obvious to express the polypeptide of claim 1 in such yeast in order to provide polypeptide having mannose moieties that would allow for effective clearance of the polypeptide.

The species recited in claims 10 and 13 are specifically taught by Goochee et al. at page 1348. The species recited in claim 29 is not specifically taught at page 1348; however, Goochee et al. teach most yeast strains provide such mannose moieties and it would have been within the ordinary skill of one in the art to determine which yeast species and strains would be appropriate.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, Ph.D., whose telephone number is (703) 308-3976. The examiner can normally be reached on M-F from 8:15 a.m. to 4:45 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

D. Saunders:jmr

Jan. 3, 2002

Jan. 4, 2002

David A Saunders

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ART UNIT ~~182~~ 1644